

REMARKS

At the outset, Applicants and their representative wish to thank Examiner Wang for the interview held on July 1, 2003. During the interview, a number of issues were clarified, which have helped Applicants to more fully address the concerns of the Examiner. Applicants thank Examiner Wang for his time and the courtesy of extending the interview.

Claims 60-62, 64-72 and 74-111 are pending the application and presented for examination. Claims 60, 70, 74, 81, 91, 95, and 103-104 have been amended. Claims 107-111 are newly added.

Support for the amendment to the claims and new claims is found throughout the specification as originally filed. More particularly, support for the amendments to claims 60, 70, 81, 91 and 104 is found, *inter alia*, at page 8, line 9 and at page 16, line 15 of the specification. As disclosed therein, the upper threshold of sodium nitroprusside when used in the present invention is about 200  $\mu$ g or less. As the molecular weight of sodium nitroprusside is 297.95  $\mu$ g/ $\mu$ mole, this amount represents about 0.67  $\mu$ moles. Further, on page 16, line 15 of the specification, a 0.2 mg Nitropatch is disclosed. The active agent of the Nitropatch is nitroglycerin. As the molecular weight of nitroglycerin is 227.09  $\mu$ g/ $\mu$ mole, this amount represents about 0.88  $\mu$ moles. Support for the amendments in claims 74 and 95 is found, for example, on page 9, line 4. The amendment to claim 103 corrects a typographical error. Support for new claim 107 is found, for example, on page 7, lines 27-29. Support for new claims 108-111 is found, for example, on page 7, lines 26-27, bridging to page 8, lines 1-2; and page 16, lines 2-6. A dosage of 5-20  $\mu$ g of PGE1 represents about 0.0141-0.0564  $\mu$ moles of PGE1, as the molecular weight of PGE1 is 354.5  $\mu$ g/ $\mu$ mole. This range of PGE1 (5, 10, 15 and 20  $\mu$ g), together with a combination of 50  $\mu$ g of SNP, represents a combination mole ratio of 1:12; 1:6; 1:4 and 1:3, respectively. As such, no new matter has been introduced with the foregoing amendments and new claims. Reconsideration is respectfully requested.

**I. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

Claims 60-62, 64-72 and 74-80 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. According to the Office Action, the term "low" in claims 60 and 70 is a relative term which renders the claim indefinite. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Applicants have amended the claims to recite preferred specific ranges of the at least one NO producing agent. Applicants believe that by reciting these specific amounts, the claims are unambiguously clear and definite. As such, Applicants respectfully request that the rejection be withdrawn.

**II. REJECTION UNDER 35 U.S.C. § 102(e)**

Claims 60, 61, 63-71 and 73-80 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,849,803 ("Kock *et al.*"). According to the Examiner, Kock *et al.* allegedly teach a method for treatment of erectile dysfunction by administering to the patient nitroglycerin along with prostaglandin. The Examiner acknowledges that Kock *et al.* do **not** teach that the methods would be less painful compared with the method wherein prostaglandin is employed alone. However, the Office Action alleges that such properties are considered *inherently* possessed by the prior art. In response, Applicants respectfully traverse the rejection.

**A. The asserted inherency must be certain.**

As the Examiner is well aware, the asserted inherency must be based in fact or technical reasoning "to support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP §2112.

Kock *et al.* teach administration of large doses (*e.g.*, 0.5 to 5 mg) of nitroglycerin to treat erectile dysfunction. Kock *et al.* disclose that such doses are *very high* compared to the dose of nitroglycerin normally given to angina pectoris patients

(*see*, col. 3, lines 22-24, Kock *et al.*). In particular, Kock *et al.* teach a dose range of 0.5 to 5 mg, preferably, 0.5 to 2.5 mg of nitroglycerin alone or in combination with another agent to treat impotence (*see*, col. 3, lines 20-22 and Table 1 at col. 4, 5 and 6, Kock *et al.*). Kock *et al.* teach that these dosages produce a penile erectile response, and a further systemic effect of a drop in blood pressure (*see*, notes below Table I, columns 5 and 6).

In stark contrast, the present invention sets forth:

60. A method of decreasing pain associated with use of prostaglandins for treatment of erectile tissue dysfunction comprising administering to a subject in need of prostaglandin at least one NO producing agent **at a low dose** which does not produce significant systemic side effects, but which decreases pain associated with prostaglandin use, wherein said low dose of said at least one NO producing agent is a unit dose of about 0.88  $\mu$ mole or less.

The use of a **low dose** which does not produce significant systemic side effects, but which decreases pain associated with prostaglandin use **does not** "necessarily flow" from the teaching of Kock *et al.* In fact, the low dose of at least one NO producing agent is **not** effective *to produce a pharmacologically induced erection*. The present invention provides dosages of NO producing agents which are about one half to about one twentieth of those known to induce vasodilation in "normal" circulations. Further, these low doses of NO producing agents exert no systemic effect in normal vasculature. Treatment with an NO provider according to the present invention does **not** directly modulate the erectile response by directly causing vascular smooth muscle relaxation such that there is an immediate erectile response, because the NO producing agent is administered at a dosage that is much lower than required to directly effect a systemic response.

Thus, the allegedly inherent characteristic does not "necessarily flow" from the teachings of the applied art, because no where does Kock *et al.* teach a **low dose** which does not produce significant systemic side effects, but which decreases pain associated with prostaglandin use. Further, Kock *et al.* does not teach a dose of an NO

producing agent that is not effective to produce a pharmacologically induced erection. Therefore, this reference does not anticipate the claims.

**B. The asserted inherency must be recognized by one of skill**

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

A person of ordinary skill would not recognize that the low dose of an NO agent as presently taught and claimed would be effective to decease pain. Prior to the advent of the present invention, conventional wisdom was such that prostaglandin use results in pain. For example, the specification sets forth on page 3, lines 17, bridging to page 4, lines 1-3 the following:

[i]t is now known and has been documented in the literature that a single use of prostaglandin E1 (PGE1) produces a **pain** response in about 3 to 10 percent of individuals using this therapy. However, it also known that over time the repeated use of PGE1 is associated with a **continuing incidence of pain**. This is such that 40 to 45 percent of patients using PGE1 multiple times will report a **pain response** with use (Linet *et al.*, NEJM, Vol 334 (14) 873 (1996)). When such patients use PGE1 for a prolonged period of time, they expect that they may experience **pain** and this becomes a serious problem which may result in decreased use of PGE1 or switching to an alternative therapy. Alternatives currently include surgical intervention (destructive and irreversible, with a success rate between 31 to 80 percent); vacuum devices (moderate efficacy, may be difficult for some men to use and may cause penile trauma); and oral medications (unproven efficacy). Transurethral administration of PGE1 or other vasoactive agents is another alternative approach to injection therapy, although it has resulted in report of penile pain in 35.7 percent of men who attended for clinic testing (Padma-Nathan *et al*, NEJM, Vol. 336(1): 1 (1997)).

Thus, extrinsic evidence teaches that prostaglandin use is painful.

Therefore, the missing descriptive matter (or inherent characteristic i.e., "no pain") is **not** necessarily present in the thing described because an ordinary skilled artisan would not appreciate that prostaglandin could be used without pain. This is supported by the conventional wisdom and scientific literature. Contrary to the Examiner's statement that the method steps are the same, the instant invention recites a low dose of an NO agent that **decreases pain** associated with prostaglandin use. As such, the silent characteristic "or gap" in the reference cannot be filled with recourse to extrinsic evidence.

Clearly, Kock *et al.* provide no teaching of administration of an NO producing agent in combination with prostaglandins at a low dose which does not produce significant systemic side effects but which decreases pain associated with prostaglandin use. Thus, this reference does not anticipate the claim. As such, withdrawal of this rejection under 35 U.S.C. § 102(e) is respectfully requested.

### III. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 60-62, 64-72 and 74-106 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kock *et al.* in view of Akkus *et al.*, Medline Abstract, ("Akkus *et al.*"), AN 95174112 and PCT Publication No. WO 94/04120 ("Cesar *et al.*"). According to the Office Action, it would have been obvious to one of skill in the art to employ lower amounts of nitroglycerin in treating sexual dysfunction, or to employ the combination for treating female sexual dysfunction. In response, Applicants respectfully traverse the rejection.

As set forth in M.P.E.P. § 2143,

[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed

combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure.

*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)

**1. There is no suggestion or motivation to modify the references**

As the Examiner is aware, obviousness can only be established by combining or modifying the teachings of the cited art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

Kock *et al.* teach a high dose range of 0.5 to 5 mg, preferably 0.5 to 2.5 mg of nitroglycerin alone or in combination with another agent to treat impotence. Kock *et al.* do not teach or suggest the use of an agent that augments cGMP at a dose which does not produce significant side effects would be useful in decreasing the pain associated with prostaglandin administration. Accordingly, this reference fails to provide any motivation to modify the teaching to produce the claimed invention.

The teachings of Akkus *et al.* does not supplement the deficiencies of Kock *et al.* The Abstract by Akkus *et al.* is merely a report of an "unusual case" of clitorimegaly wherein intracorporeal injection of prostaglandin E1 resulted in marked clitoral erection. There is no discussion whatsoever of administration of a NO producing agent or an agent that augments cGMP.

Cesar *et al.* teach the use of histamine H2 receptor agonists and/or histamine H3 receptor agonists for treatment of erectile dysfunction in animals, particularly humans. Use of NO producing agents to treat male impotence is discussed in the background section of this reference. The NO producing agent, SIN, is disclosed as being considerably less effective than PGE1 and is taught not to play a role in the management of male impotence. There is no other disclosure of NO producing agents in this reference. Furthermore, there is no teaching or suggestion of using an agent at a low dose which does not produce significant systemic side effects but which decreases pain

associated with prostaglandin use. Thus, the teachings of Cesar *et al.* does not supplement the deficiencies of Kock *et al.*

Applicants assert that the secondary references fail to remedy the deficiencies of the primary reference cited in this rejection. The combination of references simply do not teach a low dose of an NO agent to decrease the pain associated with prostaglandin administration for erectile dysfunction. Thus, a *prima facie* case of obviousness has not been established. As such, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

## 2. There is no reasonable expectation of success

There is no reasonable expectation of success that the modification that the Examiner contemplates will succeed. “Both the suggestion and the expectation of success must be found in the prior art, not the Applicant’s disclosure.” *In re Dow Chem. Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

As discussed above, Kock *et al.* teach a **high dose** range of 0.5 to 5 mg, preferably 0.5 to 2.5 mg of nitroglycerin alone or in combination with another agent to treat impotence.

Kock *et al.* teach at column 3, lines 17-23:

When nitroglycerine is used as the active substance it should be administered in a dose not exceeding 5 mg per urethra because of the risk of blood-pressure fall. The dose range according to the invention is 0.5-5 mg, preferably 0.5-2.5 mg. This dose, however, is **very high** compared to the dose of nitroglycerine normally given to Angina pectoris patients which is 0.25 mg to 0.5 mg. [Emphasis added].

The Examiner states:

Kock *et al.* do not teach a particular low limit of amounts of nitroglycerine. Further note Kock *et al.* particularly teach an **intraurethral administration, which generally requires much higher dosage compared with other administrating route.** [Emphasis added].

The Examiner implies that a skilled person would be motivated to use a *lower dose* for erectile dysfunction treatment as intraurethral administration requires much *higher doses* than other modes of administration. Thus, the Examiner uses the route of administration of Kock *et al.* as motivation to use lower amounts. Applicants respectfully disagree.

The urethra is composed of a *mucous membrane*, supported by a submucous tissue which connects it with the various structures through which it passes. Thus, a drug applied to the urethra would be absorbed *transmucosally* rather than for example, *transdermally*. Thus, contrary to the Examiner's statement that "intraurethral administration... requires much higher dosages compared with other administrating routes," it is known for example, that *mucous membranes* permit topically applied drugs ready access to the *systemic circulation*, whereas skin is relatively impermeable. As nitroglycerin is known to be readily absorbed percutaneously, it would follow that a skilled person would realize that *higher doses* as taught by Kock *et al.* are necessary to ensure the local effect of an erection that Kock *et al.* seeks to achieve..

Kock *et al.* explicitly states the use of a dose which is much higher than would be used for angina pectoris patients. A transmucosal route of therapeutic administration is an effective *systemic route* of administration. Thus, a skilled artisan would expect that transmucosal delivery of nitroglycerin intended to produce a local effect as taught by Kock *et al.* requires a larger dose than a dose that is effective to treat angina such as a sublingual dose<sup>1</sup> (another transmucosal route commonly used by angina patients), because transurethral administration is close to its intended site of action.

Thus, given the explicit teaching of Kock *et al.*, Applicants have proceeded against conventional wisdom. Proceeding contrary to accepted wisdom is evidence of nonobviousness. The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re*

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<sup>1</sup> The suggested dose for a sublingual spray is 1-3 sprays over 15 minutes with each spray delivering 0.4 mg NTG, which equals a total dose of 0.4 mg to 1.2 mg over a period of 15 minutes.

*Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986) MPEP § 2145. *Kock et al.* teaches that *a high dose* by transmucosal delivery is necessary to achieve a local effect. Applicants have proceeded contrary to accepted wisdom by using *a low dose*, which is evidence of nonobviousness. Therefore, Applicants respectfully request that the Examiner withdraw the rejection.

**3. The prior art references do not teach or suggest all the claim limitations**

The prior art references or combination of references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicants assert that the prior art references do not teach or suggest all the limitations of the claims.

*Kock et al.* teach administration of large doses (e.g., 0.5 to 5 mg) of nitroglycerin to treat erectile dysfunction, such doses are very high compared to the dose of nitroglycerin normally given to angina pectoris patients (*see*, col. 3, lines 22-24, the '803 patent). *Kock et al.* teach that these dosages produce a penile erectile response, and a further systemic effect of a drop in blood pressure (see notes below Table I, columns 5 and 6).

In contrast, the present invention provides dosages of NO producing agents which are about one half to about one twentieth of those known to induce vasodilation in "normal" circulations. These low doses of NO producing agents exert no systemic effect in normal vasculature. Treatment with an NO provider according to the present invention does *not* directly modulate the erectile response by directly causing vascular smooth muscle relaxation such that there is an immediate erectile response, because the NO producing agent is administered at a dosage which is much *lower* than required to directly effect a systemic response.

As the prior art references or combination of references do not teach or suggest all the limitations of the claims, Applicants assert that a *prima facie* case of

obviousness has not been established and respectfully request that the Examiner withdraw the obviousness rejection.

**IV. CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder  
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP  
Two Embarcadero Center, 8<sup>th</sup> Floor  
San Francisco, California 94111-3834  
Tel: 925-472-5000  
Fax: 415-576-0300  
JS:slw  
59055924 v2